Using stem cell-derived gametes for same-sex reproduction

PAPER

Using stem cell-derived gametes for same-sex reproduction: an alternative scenario

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ABSTRACT

It has been suggested that future application of stem-cell derived gametes (SCD-gametes) might lead to the possibility for same-sex couples to have genetically related children. Still, for this to become possible, the technique of gamete derivation and techniques of reprogramming somatic cells to a pluripotent state (directly or via somatic cell nuclear transfer) would have to be perfected. Moreover, egg cells would have to be derived from male cells and sperm cells from female cells, which is believed to be particularly difficult, if not impossible. We suggest a more plausible scenario to provide same-sex couples with the possibility to parent a child who is genetically related to both parents. Although technical feasibility is an advantage (also in terms of safety), disadvantages are that cooperation of a donor of the opposite sex is still required and that the partners are genetically linked to the resulting child in a different degree. However, since in our scenario the donor's genetic contribution would not outweigh any of the parents' genetic contribution, this alternative route may ease the fear for a possible parental claim by the donor. Like many other applications in the field of infertility treatment, the goal to create SCD-gametes for reproductive purposes is largely based on the high value attributed to genetic parenthood. Although we believe that genetic relatedness is neither a necessary nor a sufficient condition for 'good' parenthood, we do believe that many people may consider our scenario a welcome alternative.

INTRODUCTION

The normative ideal of 'normal' parenthood requires that both partners contribute 50% of the child's genes. Through the years, scientific efforts have been made to assist people in reaching this ideal. Several examples from the field of infertility treatment illustrate how genetics serves as a criterion for attributing parenthood.[1 2] Treatments which lead to (partially) unrelated offspring are considered second best to services which do establish a genetic link, even if those services are riskier and more costly. The creation of patient-specific stem cell-derived gametes (SCD-gametes) for reproductive purposes is one of the most recent steps in this direction. It is believed that SCD-gametes may create opportunities for heterosexual couples who are biologically unable to have genetically related children as well as for same-sex couples who desire to parent a genetically related child. Currently, the closest same-sex couples can come to shared genetic parenthood, is via 'symbolic gestures', such as reception of oocytes from partner, or intrafamilial gamete donation to establish a genetic link with the child.[1 3–6] In theory, lesbian couples could also consider mitochondrial replacement so that one mother provides the nuclear DNA and the other the mitochondrial DNA.[7]

It has been suggested that SCD-gametes may provide an emancipatory outcome as a route to 'full genetic parenthood'.[8] If it would become possible to generate oocytes from men, and sperm from women, same-sex couples would be able to have offspring that is genetically related to both parents: the 'derived' gamete from one partner could be combined with the 'natural' gamete of the other partner. If clinically available, it would be unjust to exclude same-sex couples from using this technology based on their sexual orientation, or because it would be 'unnatural'. Fears about the welfare of children parented by same-sex couples are ungrounded,[3] and the natural as such is morally neutral, so labelling something as 'unnatural' is not a convincing moral argument.

It is, however, contested whether it will be possible to produce gametes from the opposite sex and thus for same-sex couples to parent a child to which each partner makes an equal genetic contribution. Especially the possibility of deriving male gametes from female cells is heavily contested (see below). Also, even if technically possible, this procedure would require more extensive manipulations than 'regular' gamete derivation from stem cells and thus holds even more risks for the welfare of the future offspring (see below).

We believe that same-sex couples are being given false hope about the prospect of being able to create a child who shares 50% of its DNA with both partners. However, if genetic relatedness (sharing a substantial amount of (nuclear) DNA, but not 50%) and legitimacy as a parent are sought, rather than 'full genetic parenthood' (sharing 50% of DNA), SCD-gametes might be ready for the clinic sooner for same-sex couples than for heterosexual couples. In this paper, we describe a more practical alternative for same-sex couples to conceive a child that shares 50% of DNA with one partner, 25% with the other partner and 25% with a donor, without the necessity of producing 'patient-matched' pluripotent stem cells or deriving male gametes from female cells or vice versa.

We explore the possibility of 'full' genetic parenthood for both same-sex parents, followed by the alternative scenario which we primarily elaborate as a possibility for lesbian couples. It is important to note that—as Mertes has previously argued—the entire enterprise of gamete derivation to establish

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genetic parenthood reinforces the importance accorded to genetic relatedness, thus strengthening the very 'problem' that it is meant to solve.[9] It can be asked if, instead of considering solutions including the alternative described here, it would not be better to fundamentally question the importance of a genetic link for family building as well as the use of sophisticated forms of medically assisted reproduction as a means to providing that link. Although we sympathise with this perspective, the preference for a genetically related child seems too much a matter both of evolutionary biology and culture to think it is realistic to expect that it can simply be set aside as a result of rational debate. Inevitably, this means that would-be parents including same-sex couples will have to make their reproductive decisions in a context where genetic relatedness is regarded as important, and where the lack of it has direct implications. This may, for instance, induce the idea that because of the genetic link with the child a greater parental status could be attributed to the donor than to the non-genetically related parent (both by the child, the social parent and the donor), which could raise fears that the donor might intervene in the family. We wish to describe our scenario as a possible alternative and to initiate ethical debate about it.

SCD-GAMETES

Several pathways have been explored to obtain SCD-gametes, but most of the attention has gone to gamete derivation from embryonic stem cells (ESCs) and from induced pluripotent stem cells (iPSCs). ESCs derived from the inner cell mass of blastocysts have the ability to differentiate into all body cells, including into germ cells.[8] When ESC-derived gametes are to be used for reproduction leading to full genetic parenthood, this would require the creation (and destruction) of an embryo through somatic cell nuclear transfer (SCNT). Alternatively, iPSC-derived gametes avoid the use of embryos. By reprogramming somatic cells, iPSCs can be obtained which may then be differentiated into gametes.

According to Easley *et al*,[10] however, SCD-gametes are still 'far from any direct clinical application'. Although Hendriks *et al*[8] believe that these studies 'seem to be progressing steadily towards possible future clinical application', they underline that the current findings are still preliminary and that overall efficiency has to be considerably improved. Obstacles such as the epigenetic stability of the SCD-gametes and concerns about the health of future offspring have to be overcome if SCD-gametes are to be used for infertility treatment.[8 11] Moreover, to produce patient-specific gametes, the technique of deriving iPSCs or that of SCNT would have to be improved.[2] There is ongoing discussion about possible tumorigenicity of iPSCs as well as about increased risks for accumulation of chromosomal aneuploidies.[11] There is also no consensus about reprogramming and validation methods to obtain iPSCs.[12] SCNT, on the other hand, is regarded as a more efficient technique, although it is uncertain whether SCNT-ESCs are any better than iPSCs.[13]

As mentioned above, even more scepticism is directed towards the potential use of SCD-gametes in same-sex reproduction, since this requires the production of sperm from women and eggs from men. Little research has been directed towards this goal and still less has been achieved.[8 11] The Hinxton Group concluded that it is 'not likely in the future of the science' that SCD-gametes will be used in same-sex reproduction due to 'significant if not insurmountable scientific barriers'.[14] They stated that it will be very difficult to derive usable eggs from men and that due to biological and technical reasons it may even be 'impossible, to derive sperm that could be used for reproduction from XX (chromosomally female) cells'.[15] Thus, it is believed that lesbian couples will not be able to benefit from this technology because no sperm can be generated in the absence of paternally imprinted genes. This was the reason to think of a more likely alternative, especially for lesbian couples.

AN ALTERNATIVE METHOD

Due to technical challenges to derive gametes from the opposite sex, the possibility for same-sex couples to parent a child who shares 50% of her genes with both parents seems quite a long way off. Instead, it might be more likely to derive gametes from embryos that were created by fertilisation, rather than deriving gametes from SCNT-ESCs or iPSCs. This route is presumably less complicated and less risky. Zhou *et al*[16] produced the first generation of functional spermatids from murine ESCs, conforming to the 'gold standards' of in vitro-derived germ cells. By means of intracytoplasmic sperm injection (ICSI), these 'spermatid-like cells' successfully fertilised oocytes, resulting in viable, fertile offspring that gave birth to the next generation.[16] These are promising results that may lead to interesting clinical applications. For same-sex couples, this may yield the more realistic possibility to draw a donor into the process of obtaining SCD-gametes to beget a child which is genetically related to both partners. Consider the following scenario:

> A lesbian couple, W_1 and W_2 share the wish to parent 'their own', genetically related child. Suppose that it would be possible to derive sperm from human ESCs. Through ICSI a 'male' embryo—E_1—could be generated by combining W_1's oocytes with the sperm of a genetically unrelated donor, D. E_1 shares a 50% genetic linkage with W_1 and with D. ESCs could be derived from E_1 and differentiated into sperm cells. This sperm could then be used to fertilize an oocyte of W_2. The resulting embryo, E_2, would then share 50% of its genes with W_2 and 50% with E_1, which on its part has a 50% genetic relatedness to both biological progenitors W_1 and D. This would still make E_2 genetically related to D for an average of 25%, and as much to its future mother W_1. A similar scenario would be possible for two male partners, although then surrogacy is required.

This situation is similar to cases in which W_2 would be inseminated by the brother of W_1 in the sense that there would also be an average 25% overlap in the genomes of W_1 and the resulting child. The difference is that in the case of intrafamilial gamete donation, the donor has a much stronger genetic link to the child (50%) than W_1. The rationale behind intrafamilial gamete donation often points back to the value attributed to genetic relatedness.[1] The underlying idea is that if it is impossible to share 50% of one's genes with a future child, then '25% is better than nothing'.[5] The fact that intrafamilial donation is accepted, common and increasing suggests that people will be interested in our scenario.[17] It may thus be likely that lesbian couples would be willing to engage in such a scenario. A further reason for thinking this is that our scenario would be a better alternative for those couples who value a genetic link with the child for both partners and who would be weary of parental claims by the donor.[18] This scenario may generally avoid that the donor will be attributed a greater parental status than the non-genetically related parent (either by the child, W_1 or the donor himself) on the basis of his genetic contribution. Since the resulting child would inherit 25% of W_1's DNA, her status would no longer be 'limited' to that of social mother, which might comfort her fears to be sidelined by the donor. Importantly, as parenthood is not limited to genetic contribution, W_1's intention to be a parent and her social role as a

parent would rank her higher than D on the imaginary list of candidate parents, although the genetic contribution of both W_1 and D would be the same, namely about 25%.

Surprisingly, the described alternative has hardly received any attention in the literature, although it is less futuristic than some of the scenarios that have been suggested.[19]

BALANCING PROCREATIVE AUTONOMY AGAINST OTHER INTERESTS

If we take the high value attributed to genetic parenthood as a given, this alternative seems plausible for lesbian couples. However, this premise is not uncontroversial. Our scenario may be regarded as yet another instance of how the value attributed to genetic parenthood leads to the development of new routes to achieve it, which—in turn—reinforces the presumed importance of genetic relatedness. Although we believe that having a genetic relationship with one's children is neither a necessary nor a sufficient condition for a good parental relationship, we do not think that this settles the issue of the ethical acceptability of our scenario.[9] The issue is whether, against the background of the de facto importance given in society to the genetic link, the benefits that this scenario may have for lesbian couples are proportionate to the ethical concerns it may also raise, including the concern about 'reinforcement'. This does not imply that such reinforcement is unproblematic. However, denying would-be lesbian parents the possibility to have genetically related offspring—for whom this is important because of the reason we discussed above—is not the way to bring about the ideal of a society where genetic parenthood is not considered superior. Also, if one considers the 'reinforcement argument' a sufficient reason to dismiss our scenario, consistency requires that one should also dismiss, say, ICSI for men when sperm donation is available.

A second ethical concern is the controversial issue of sacrificing E_1 for the sake of genetic relatedness. Even if one does not ascribe an absolute moral status to embryos, one need not accept that embryos are being sacrificed for whichever purpose. Particularly, the intentional creation and destruction of embryos is regarded by many as disrespectful to human life and only permissible for exceptionally important causes. Only if one believes that the creation of SCD-gametes for the sake of genetic relatedness outweighs the cons of creating and destroying embryos, can the discussed scenario be considered acceptable. By the same token, the general venture to create patient-specific SCD-gametes would be discredited, unless the iPSC route is perfected. It can also be argued that if embryo destruction is accepted in the context of *in vitro* fertilisation (IVF), additional reasons will be needed to deny this acceptability in the context of reproduction via SCD-gametes. The related argument that it would be unacceptable that E_1 cannot consent to being a gamete donor (hence genetic parent) is undermined by the fact that E_1 will not develop into an autonomous person, while informed consent is meant to respect personal autonomy.

Third, although less complicated and likely safer than the SCNT or iPSC routes, it is still an important prerequisite for any application that the technology is safe. The level of technological intervention will always remain very high, which necessitates thorough preclinical research prior to clinical use to minimise safety risks. For two women, our scenario would require (minimally, in case of 100% efficiency of all steps) two cycles of ovarian stimulation, sperm donor recruitment and sperm collection, two cycles of ICSI, of which one combined with pre-implantation genetic diagnosis (to determine the sex of the created embryos), ESC derivation, ESC line culturing, sperm derivation from ESCs and embryo transfer. We leave it open for discussion whether or not such a scenario is likely to ever meet the requirements of good clinical practice due to the accumulation of possible safety risks in each of these steps which have to be weighed against the benefits of our scenario. The desirability and acceptability of our scenario will depend substantially on the point of reference that is adopted. Compared with the speculative prospect of deriving female sperm or male oocytes via induced pluripotency or SCNT, our scenario is safer and more feasible, but the genetic link is weaker and a donor is still involved. Compared with donor conception, our scenario is less safe, less feasible, but the 'second' mother has a genetic link that is as strong as the donor's genetic link to the child.

There might also be psychological concerns: it may be a source of discomfort for the resulting child to know that E_1 had to be destroyed for her to live, or because she has never known E_1, especially if this embryo is conceptualised as a 'parent'.[20 21] Similar arguments have been used with regard to the possible reproductive use of oocytes from aborted foetuses. Fact is that we do not really know what the effects will be on the psychological well-being of the resulting offspring. It would be reasonable not to exaggerate these concerns since similar concerns from the past (eg, about IVF and donor conception) have not been confirmed. Much will depend on how these new technologies are explained to the children and portrayed in the media. In any case, it is not unique to the use of SCD-gametes that the well-being of the future offspring is weighed against the parents' desire for genetic parenthood.[22]

It has also been questioned whether genetic relatedness is important enough to justify the use of costlier and more risky techniques such as ICSI, mitochondrial donation and now SCD-gametes.[23] Indeed, a large part of the field of assisted reproductive technology seems to be based on the self-evident importance of a genetic link between a child and her parents without questioning whether the effort of developing such techniques is in proportion to the goal of having a genetically related child.[2] Given the context of finite resources, this should involve considerations about just resource allocation and opportunity costs of investing in more urgent interventions. Again, however, this concern is not unique to our scenario.

DO THE MEANS SERVE THE END?

If the goal of producing SCD-gametes is to establish genetic parenthood, we should deliberate whether or not this goal is acceptable in view of the issues explored above, and we should also critically assess whether or not the goal is reached at all. Do SCD-gametes lead to genetic parenthood? People value the idea of a child sharing the parents' DNA, but the concept of genetic parenthood is not limited to this criterion.[9] If this were so, identical twins would be thought of as the parents of each other's children. Moreover, if a genetic link is important, then how much would be enough? From the context of mitochondrial donation, it may seem that a very tiny contribution of DNA would be enough to be regarded as a genetic parent, since children born following mitochondrial replacement are frequently called 'three-parent babies'.[7] Reason for this is that they receive nuclear DNA from the man and the woman, and mitochondrial DNA from the oocyte donor, however limited it may be. Would W_1's 25% genetic contribution—which is clearly larger than the contribution of mitochondrial DNA—then be enough to make her a genetic parent of E_2? This will depend on whether a broad or narrow definition of genetic parenthood is applied, but a strong argument against would be that the progenitors with whom we share an average of 25% of DNA in natural

conception are grandparents, not parents. Also, despite being 'not more than a ball of 150 cells' E_1 may thus be considered an extra generation.[20] Thus, if a narrow conception of genetic parenthood (sharing 50% of DNA) is adopted, then our scenario does not reach its goal for W_1, although it will establish a substantial genetic link with the future child.

However, establishing 'full' genetic parenthood may not be the primary concern here. As mentioned earlier, the more important goal may be to outrank other candidate parents and thus increase the legitimacy as a parent. In our scenario, W_1 is a genetic progenitor of E_2 and will be second on the imaginary list of candidate parents (after W_2, whose status as a parent is incontestable). This position, together with her role as the social parent, the intended parent and possibly as the gestational mother considerably strengthens her parental role and will comfort her fear to be sidelined by the donor. This substantial benefit could contribute to the willingness to go to great lengths to minimise the donor's genetic contribution.

This is a good moral reason in favour of this scenario, but it is not a sufficient argument for it to be pursued, given the safety risks, the opportunity costs and the contested importance of genetic parenthood. While genetic relatedness is highly valued in parent–child relationships, endeavours to achieve it are morally controversial (as this paper illustrates) and might, at the same time, reinforce the dogma of genetic relatedness. However, this reinforcement does not contradict that precisely because of the strong societal emphasis on genetic relatedness, lesbian couples who wish to parent a child have an interest in minimising the genetic contribution by the donor as much as possible. Thus, it may be reasonable to argue that our scenario is proportionate to this interest, provided that it would be safe and despite the fact that it inherently involves the creation and destruction of embryos.

CONCLUSION

The value attributed to genetic parenthood, which may be equally influenced by new reproductive technologies, leads to new constructions to accommodate the pursuit of genetic parenthood. The alternative discussed here may be regarded as such an example. On the one hand, we believe that genetic relatedness is neither a necessary nor a sufficient condition for 'good' parenthood. On the other hand, we do realise that many people prefer to pass on their DNA to their children and that genetic parenthood is widely perceived as an uncontested form of parenthood, and therefore renders legitimacy to the parental role. Our scenario would therefore be a welcome alternative for lesbian couples, since the donor's genetic contribution would not outweigh any of the mothers' genetic contribution, which would ease the fear of being sidelined by the donor. While our scenario 'only' upholds the prospect of a 25% linkage, it is nevertheless more realistic than other scenarios that have been presented in the literature. It is plausible to assume that gamete generation from human ESCs (as opposed to SCNT-ESCs or iPSCs) will be the first step to clinical applications. Thus—ironically—same-sex couples may benefit from SCD-gametes before heterosexual couples do.

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REFERENCES

1 Hendriks S, Dondorp W, de Wert G, *et al*. Potential consequences of clinical application of artificial gametes: a systematic review of stakeholder views. *Hum Reprod Update* 2015;21:297–309.
2 Cutas D, Dondorp W, Swierstra T, *et al*. Artificial gametes: perspectives of geneticists, ethicists and representatives of potential users. *Med Health Care Philos* 2014;17:339–45.
3 Murphy TF. The meaning of synthetic gametes for gay and lesbian people and bioethics too. *J Med Ethics* 2014;40:762–5.
4 Dondorp WJ, de Wert GM, Janssens PM. Shared lesbian motherhood: a challenge of established concepts and frameworks. *Hum Reprod* 2010;25:812–14.
5 Pennings G. Incest, gamete donation by siblings and the importance of the genetic link. *Reprod Biomed Online* 2002;4:13–15.
6 de Wert G, Dondorp W, Pennings G, *et al*. Intrafamilial medically assisted reproduction. *Hum Reprod* 2011;26:504–9.
7 Baylis F. The ethics of creating children with three genetic parents. *Reprod Biomed Online* 2013;26:531–4.
8 Hendriks S, Dancet EA, van Pelt AM. Artificial gametes: a systematic review of biological progress towards clinical application. *Hum Reprod Update* 2015;21:285–96.
9 Mertes H. Gamete derivation from stem cells: revisiting the concept of genetic parenthood. *J Med Ethics* 2014;40:744–7.
10 Easley CA, Phillips BT, McGuire MM, *et al*. Direct differentiation of human pluripotent stem cells into haploid spermatogenic cells. *Cell Rep* 2012;2:440–6.
11 Moreno I, Míguez-Forjan JM, Simón C. Artificial gametes from stem cells. *Clin Exp Reprod Med* 2015;42:33–44.
12 Silva M, Daheron L, Hurley H, *et al*. Generating iPSCs: translating cell reprogramming science into scalable and robust biomanufacturing strategies. *Cell Stem Cell* 2015;16:13–17.
13 Langerova A, Fulka H, Fulka J. Somatic cell nuclear transfer-derived embryonic stem cell lines in humans: pros and cons. *Cell Reprogram* 2013;15:481–3.
14 Mathews DJ, Donovan PJ, Harris J, *et al*. Pluripotent stem cell-derived gametes: truth and (potential) consequences. *Cell Stem Cell* 2009;5:11–14.
15 Hinxton Group. Consensus statement: Science, ethics and policy challenges of pluripotent stem cell-derived gametes. 2008. http://www.hinxtongroup.org/au_pscdg_cs.html (accessed 22 Jun 2016).
16 Zhou Q, Wang M, Yuan Y, *et al*. Complete meiosis from embryonic stem cell-derived germ cells in vitro. *Cell Stem Cell* 2016;18:330–40.
17 HFEA. Family donation. 2011. http://www.hfea.gov.uk/6191.html (accessed 22 Jun 2016).
18 Raes I, Van Parys H, Provoost V, *et al*. Parental (in)equality and the genetic link in lesbian families. *J Reprod Infant Psychol* 2014;32:457–68.
19 Palacios-González C, Harris J, Testa G. Multiplex parenting: IVG and the generations to come. *J Med Ethics* 2014;40:752–8.
20 Mertes H, Pennings G. Embryonic stem cell-derived gametes and genetic parenthood: a problematic relationship. *Camb Q Healthc Ethics* 2008;17:7–14.
21 Sparrow R. Orphaned at conception: the uncanny offspring of embryos. *Bioethics* 2012;26:173–81.
22 Peters PG. *How safe is safe enough? Obligations to the children of reproductive technology*. Oxford: Oxford University Press, 2004.
23 Bredenoord AL, Pennings G, Smeets HJ, *et al*. Dealing with uncertainties: ethics of prenatal diagnosis and preimplantation genetic diagnosis to prevent mitochondrial disorders. *Hum Reprod Update* 2008;14:83–94.